How Confident Should We Be?

Dear Editor:

Winkelmann et al[1] presented evidence on the usefulness of multispectral digital skin lesion analysis (MelaFind®; MELA Sciences, Inc.) as an aid in evaluating pigmented lesions (PLs) that have one or more clinical or historical characteristics of melanoma in community-based practice.[2-4] Among 137 lesions selected for biopsy, all 21 lesions with a negative test reading ("Low Disorganization") were histologically benign resulting in a negative predictive value (NPV) of 100 percent. The authors recommend that lesions with a reading of "Low Disorganization" may be considered for observation versus biopsy in the community practice setting.

A previous larger multicenter trial[3] of 160 lesions reported a NPV of 98.1 percent for the device. The difference (1.9%) between NPVs achieved in both studies was not statistically significant, but may be clinically meaningful. While multispectral analysis potentially offers a high level of diagnostic accuracy and cost savings (avoiding unnecessary biopsies), the small sample size in the Winkelmann et al[1] study limits the confidence in the true NPV (95% CI 81, 100). A NPV as low as 81 percent is within the 95 percent confidence interval.

Sensitivity to early melanoma is critical for a screening test because the cost of false negatives (undiagnosed melanoma) is far greater than that of false positives (biopsies of benign lesions). When the diagnosis of melanoma is in doubt, a low threshold for biopsy is prudent. Currently available screening tests are not 100-percent sensitive, and relying on such a device could lead to a missed melanoma. Do we want to do that?

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REFERENCES

1. Winkelmann RR, Rigel DS, Kollmann E, et al. Negative predictive value of pigmented lesion evaluation by multispectral digital skin lesion analysis in a community practice setting. *J Clin Aesthet Dermatol.* 2015;8(3):20–22.
2. Wells R, Gutkowicz-Krusin D, Veledar E, et al. Comparison of diagnostic and management sensitivity to melanoma between dermatologists and MelaFind: a pilot study. *Arch Dermatol.* 2012;148(9):1083–1084.
3. Monheit G, Cognetta AB, Ferris L, et al. The performance of MelaFind: a prospective multicenter study. *Arch Dermatol.* 2011;147(2):188–194.
4. Kupetsky EA, Ferris LK. The diagnostic evaluation of MelaFind multispectral objective computer vision system. *Expert Opin Med Diagn.* 2013;7(4):405–411.

Author's reply:

We thank Mudigonda et al for their letter regarding our recent article, "Negative predictive value of pigmented lesion evaluation by multispectral digital skin lesion analysis in a community practice setting."[1] The 100-percent negative predictive value (NPV) reported in our study was indeed from a smaller sample size (n=160 lesions) than from the article they cited in which 98.1 percent NPV was achieved with multispectral digital skin lesion analysis (MSDSLA)(MelaFind®; MELA Sciences, Inc.) from a set of 1,632 pigmented skin lesions.[2] As indicated by Mudigonda et al, the difference between these results was not statistically significant. However, Mudigonda et al failed to note that the confidence interval achieved in the referenced article with the 98.1 percent NPV (95% CI: 96.0%–100.0%) encompasses the 100-percent NPV reported in our recent article. Therefore, even with a smaller sample size, our findings are

statistically appropriate, consistent, and within the limits of the larger referenced study.

No one expects a perfect NPV in a study with a large number of cases and we of course agree that, with regards to melanoma, the cost of a false negative is far greater than a false positive. Regardless, data from reader studies have demonstrated 24-percent improvement in NPV by dermatologists using MSDSLA data compared to dermatologist biopsy decisions after clinical examination alone ($p<0.0001$).[3]

Most importantly, MSDSLA is a clinical adjunct that provides additional information for integration into the biopsy decision and not meant to be followed blindly. If the additional objective information indicates a low probability of melanoma/high-risk pigmented skin lesion, the final biopsy decision is still ultimately up to the clinical judgement of the experienced dermatologist evaluating the entire clinical picture.

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REFERENCES

1. Winkelmann RR, Rigel DS, Kollmann E, et al. Negative predictive value of pigmented lesion evaluation by multispectral digital skin lesion analysis in a community practice setting. *J Clin Aesthet Dermatol.* 2015;8(3):20–22.
2. Monheit G, Cognetta AB, Ferris L, et al. The performance of MelaFind: a prospective multicenter study. *Arch Dermatol.* 2011;147(2):188–194.
3. Winkelmann RR, Tucker N, White R, Rigel DS. Evaluating diagnostic enhancement with multi-spectral digital skin lesion analysis: a meta-analysis of 5 studies. Poster presentation: Winter Clinical Dermatology Conference; January 16–21, 2014; Kaanapali, Hawaii.

Comprehensive Tuberculosis Testing

Dear Editor:

In the article titled, "Comprehensive Tuberculosis Testing for the Dermatologist," in the April 2015 issue of *The Journal of Clinical and Aesthetic Dermatology*, Amstrong et al presented a detailed report about tuberculosis testing.[1] In this context, we wish to submit a short comment presenting our point of view and experience regarding the above-mentioned topic and prophylaxis in psoriasis patients under biologic therapy, respectively.

In Romania, according to the protocols, on initiation of biological treatment for moderate-to-severe psoriasis, all patients are screened for tuberculosis (TB) infection.[2] This consists of careful investigation of previous exposure, history and risk factors, tuberculin skin test (TST), chest radiograph, and pneumological examination. In Romania, the protocol of the Mendel-Mantoux test consisted of intradermal injection of two units of purified protein derivative (PPD) until 2013. The current protocol uses a dose of 5 tuberculin units (0.1mL). The decision to start TB chemoprophylaxis is made on the basis of the pneumological diagnosis of latent tuberculosis infection (LTBI). This diagnosis was identified through interpretation of the TST. Considering that Romania is a country with increased risk of TB infection, a positive diagnosis is signaled if a patient's PPD reaction measures 10mm or above. If there is a clinical and radiological suspicion of active TB, before the immunosuppressive therapy the QuantiFERON TB® is indicated.[3] Lighter et al[4] showed that this test can be applied to children older than two years of age to diagnose the LTBI with the same good results as in adults. Markova et al[5] demonstrated that QuantiFERON is used to survey the efficiency of the tuberculostatic treatment by measuring the amount of released interferon gamma. Katiyar et al[6] recently found that QuantiFERON has a predictive value regarding the positivity of the sputum culture after two months of intensive therapy. A positive result (>0.35UI/mL) indicates a *Mycobacterium tuberculosis* infection. Unfortunately, a differentiation between a LTBI and an active TB infection is not possible.[3] A similar situation—the difficulty to differentiate between active TB and LTBI—was presented by Solovan et al,[7] where a patient, supposed to have active TB based on TST and QuantiFERON measure, should had interrupted the biological anti TNF-α treatment, leading to exacerbation of the psoriasis.

Romania's protocol of chemoprophylaxis for LTBI at the initiation of biologic therapy consists of monotherapy with isoniazid, given daily 10mg/kg/day or 200mg/m^2 body surface area in children, 5mg/kg/day,

in adults (maximum 300mg/zi) for six months.[2] During the biological treatment, the patients are evaluated each year by performing the TST and chest X-rays.

Taking into account the high tuberculosis prevalence in Romania, the World Health Organization (WHO) recommends maintaining BCG (Bacillus Calmette-Guérin) vaccination of newborns.[8] Although this has an impact on the interpretation of the TST, the recommendation of the WHO is justified because the risk of disease and the development of severe forms of TB are high. From our experience with the psoriasis patients, we noticed that these patients have a higher positivity for TST than the vaccinated children or the individuals exposed to *M. tuberculosis*. This raises the question of the correct interpretation of TST in psoriasis patients proposed for biological treatment and the necessity of the TB chemoprophylaxis. Therefore, a more personalized protocol should be generated.

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REFERENCES

1. Amstrong F, Jordan L. Comprehensive tuberculosis testing for the dermatologist. *J Clin Aesthet Dermatol.* 2015;8(4):44–47
2. *Romanian Statistical Yearbook.* 2006; pp 69.
3. Mazurek GH, Jereb J, Lobue P, et al. Guidelines for using the QuantiFERON-TB Gold test for detecting *Mycobacterium tuberculosis* infection, United States. *MMWR Recomm Rep*. 2005:49–55.
4. Lighter J, Rigaud M, Eduardo R, et al. Latent tuberculosis diagnosis in children by using the QuantiFERON-TB Gold In-Tube test. *Pediatrics.* 2009;123:130-37
5. Markova R, Drenska R, Todorova Y, et al. Monitoring the efficacy of anti-TB therapy by using the QuantiFERON-TB Gold In Tube test. *Eur Respir Rev.* 2008;17:74–75
6. Katiyar SK, Sampath A, Bihari S, et al. Use of the QuantiFERON-TB Gold In-Tube test to monitor treatment efficacy in active pulmonary tuberculosis. *Int J Tuberc Lung Dis.* 2008;12:1146–1152.
7. Solovan C, Chiticariu E. Psoriasis, anti-tumor necrosis factor therapy, and tuberculosis: report of three challenging cases and literature review. *Infect Dis Ther.* 2013;2(1): 59–73.
8. World Health Organization. Guidance for national tuberculosis programs on the management of tuberculosis in children. WHO/HTM/TB/2006.371, WHO/FCH/CAH/2006.7. 2006.

Author's reply:

We thank Drs. Mohor and Solovan for their delineation of several insightful points regarding the management of tuberculosis testing in Romania. Given the higher incidence of the disease in Romania compared to the United States, the authors have provided a very useful contextualization of tuberculosis management which varies slightly from our country.

We thank you for your response to our article and appreciate continuing the conversation on such a pertinent topic in dermatology.

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